FOOD AND DRUG ADMINISTRATION

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

OPHTHALMIC DEVICES PANEL

Thursday,
August 1, 2002

Salons A-C
Hilton Hotel Gaithersburg
620 Perry Parkway
Gaithersburg, Maryland

FRIEDMAN & ASSOCIATES, COURT REPORTERS
11923 Parklawn Drive, Suite 203
Rockville, MD 20852
(301) 881-8132

IN ATTENDANCE:

Jayne S. Weiss, M.D., Chair

Arthur Bradley, Ph.D., Voting Member

Michael R. Grimmett, M.D., Voting Member

Alice Y. Matoba, M.D., Voting Member

Karen Bandeen-Roche, Ph.D., Consultant, deputized to vote

Stephen A. Burns, Ph.D., Consultant

Mark A. Bullimore, MCOptom, Ph.D.,
Consultant, deputized to vote

Andrew J. Huang, M.D., Consultant, deputized to vote

Leo J. Maguire, M.D., Consultant, deputized to vote

Cynthia Owsley, Ph.D., Consultant, deputized to vote

William H. Swanson, Ph.D., Consultant, deputized to vote

Glenda V. Such, M.Ed., Consumer Representative

Ronald E. McCarley, Industry Representative

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P R O C E E D I N G S (8:35 a.m.)

DR. WEISS: I'd like to call this meeting of the Ophthalmic Devices Panel to order and we'll have introductory remarks from Sarah Thornton.

MS. THORNTON: Good morning and welcome to the 104th meeting of the Ophthalmic Devices Panel.

Before we proceed with today's agenda, I have a few short announcements as usual that I'd like to make. I'd like to remind everyone out there as well as the panel and the FDA folks to sign in on the attendance sheet in the registration area just outside the meeting room here. Messages for panel members and FDA participants and information or special needs should be directed through Ms. Annmarie Williams or Ms. Jennifer Weber who are available in the registration area.

The phone number for calls to the meeting area is (301) 977-8900. In consideration of the panel, the sponsor and the agency, we ask that those of you with cell phones and pagers either turn them off or put them on vibration mode while in this room.

Lastly, will all meeting participants please speak clearly into the microphone, give your name clearly, until I get a signal from the transcriber that he no longer needs your name, so that we will have an accurate recording of your comments, please.

Now, at this time, I'd like to announce the confirmation of the new Ophthalmic Devices Panel Chair, Dr. Jayne Weiss. We also have three newly appointed voting members, Drs. Anne Coleman, Allen Ho, and Timothy McMahon, who are regrettably unable to be with us today. However, we look forward to their attendance at future meetings.

I'd also like to extend a special welcome and introduce to the public and panel and FDA staff three panel consultants who are with us for the first time today. Dr. Stephen Burns. Dr. Burns comes to us from Boston, Massachusetts, where he is a senior scientist at the Schepens Eye Research Institute and associate professor at the Harvard University. Dr. Cynthia Owsley is from Birmingham, Alabama, where she is the Professor of Ophthalmology at the School of Medicine and Co-Director of the Center for Research on Applied Gerontology at the University of Alabama. And Dr. William Swanson is a senior research scientist in the Department of Clinical Sciences at the State University of New York, College of Optometry, in New York City.

Welcome to you all. Hope you enjoy your day with us.

Will the remaining panel members take the time now to introduce themselves, and I'd like to begin with our industry rep.

MR. McCARLEY: My name's Rick McCarley. I'm the industry rep. I'm the President and CEO of Ophtec in Boca Raton, Florida.

DR. BANDEEN-ROCHE: I'm Karen Bandeen-Roche, Associate Professor of Biostatistics at Johns Hopkins University.

DR. BULLIMORE: Mark Bullimore, Associate Professor, Ohio State University.

MS. SUCH: I'm Glenda Such, consumer representative, Director of Computer Training Programs at Lighthouse International, New York City.

DR. MATOBA: I'm Alice Matoba, Associate Professor of Ophthalmology, Baylor College of Medicine.

DR. GRIMMETT: Michael Grimmett, Assistant Professor of Ophthalmology at the University of Miami, School of Medicine.

DR. WEISS: Jayne Weiss, Professor of Ophthalmology and Pathology, Kresge Eye Institute, Wayne State University, Detroit.

DR. BRADLEY: Arthur Bradley, Professor of Visual Science, Indiana University.

DR. HUANG: Andrew Huang, Associate Professor of Ophthalmology, University of Minnesota.

DR. MAGUIRE: Leo Maguire, Associate Professor of Ophthalmology, Mayo Clinic.

MR. WHIPPLE: And I'm Dave Whipple, Deputy Director of the Division of Ophthalmic, Ear, Nose and Throat Devices.

MS. THORNTON: Thank you very much.

At this time, I'd like to read the conflict of interest statement for the meeting today.

"The following announcement addresses conflict of interest issues associated with this meeting and is made part of the record to preclude even the appearance of an impropriety.

"To determine if any conflict existed, the agency reviewed the submitted agenda for this meeting and all financial interests reported by the committee participants. The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests. However, the agency has determined that participation of certain members and consultants, the need for whose services outweigh the potential conflict of interest involved, is in the best interests of the government.

"Therefore, waivers have been granted to Drs. Mark Bullimore and Stephen Burns for their interest in firms that could potentially be affected by the panel's recommendation. Dr. Bullimore's waiver allowing him to

participate fully in today's deliberations involves a consulting arrangement with a competing technology firm. For this unrelated consulting service, he receives less than $10,000 a year. Dr. Burns' limited waiver allows him to participate in the panel discussion but excludes him from voting. His interest involves a grant to his employer with a competing firm funded for less than $100,000 per year for which he has involvement in data collection and interpretation.

"Copies of these waivers may be obtained from the agency's Freedom of Information Office, Room 12A-15 of the Parklawn Building.

"We would like to note for the record that the agency took into consideration other matters regarding Drs. Arthur Bradley, Michael Grimmett, and Jayne Weiss. They reported interest in firms at issue but in matters not related to today's agenda. The agency has determined therefore that they may participate fully in all discussions.

"In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement and the exclusion will be noted for the record.

"With respect to all other participants, we ask

in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon."

I will read now the appointment to temporary voting status.

"Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27th, 1990, and as amended August 18th, 1999, I appoint the following individuals as voting members of the Ophthalmic Devices Panel for this meeting on August 1st, 2002: Dr. Karen Bandeen-Roche, Dr. Mark Bullimore, Dr. Andrew Huang, Dr. Leo Maguire, Dr. Cynthia Owsley, Dr. William Swanson. For the record, these individuals are special government employees and consultants to this panel or other panels under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting." Signed Dr. David W. Feigal, Jr., Director of the Center for Devices and Radiological Health, dated July 19th, 2002.

Thank you, Dr. Weiss.

DR. WEISS: Thank you, Sally.

We will now start the open public hearing. There are three individuals who have requested to speak

before us. I would appreciate when they approach the podium, they should identify themselves and any financial conflicts or potential conflicts, and we'll start with Mr. Ron Link. If you could come to the podium and read your statement, please?

MR. LINK: Good morning.

My name's Ron Link. I'm Executive Director of Surgical Eyes, Tampa, Florida. I have no conflict of interests with regard to this meeting.

Well, good morning, Ophthalmic Devices Panel members and members of the audience. I'm here today to advocate on behalf of thousands of people who have longstanding complications of refractive surgery. Together, we can confront the challenge of rehabilitation of as many of these people as possible. Surgical Eyes supports the advancement of wavefront technology in that it may hold promise for the visual rehabilitation of these patients who live with complications of LASIK and other refractive surgeries. No less important is our mutual obligation that fewer patients with complications be created.

I want to reference this slide of a recent survey that we did at Surgical Eyes, only ran for a week, but I think the results are compelling. This first slide were LASIK successes in the sense that they had 20/40 or

better UCVA. You can see significant quality of vision issues and you expect much more in the excellent categories, but we see that's not the case across different lighting conditions. Now, attempts to improve that vision with contact lenses or glasses yielded slight improvement. So what this tells me is that we need better technologies to rehabilitate these folks. Now, people who were not corrected to 20/40 or better had even less good result with the attempts at correction.

These people and many others at Surgical Eyes may very well benefit from laser and contact lens wavefront technology. If the panel votes for approval on the PMA for this device, we ask that it do so with the following conditions.

Number 1. Controlled studies on post-refractive eyes. Clinical studies at multiple sites across the United States on post-refractive eyes with a minimum one-month follow-up. Anecdotal reports from the estimated 200 global cases of wavefront-guided treatments on patients with complications reveal that results are often immediate. Clinical studies should not only include those with under-corrections or smaller aberrations. Decentration, central islands, disparity between the affected optical zone and pupil size, these and other complications result in higher-order aberrations. We believe wavefront treatment on such

patients should first be performed in controlled circumstances by surgeons who have the requisite skill and technical experience to perform therapeutic studies on post-refractive eyes.

Controlled studies are necessary to prevent a rush by patients and doctors alike to avail themselves of a new device in off-label use without the necessary specific clinical protocols and data analysis to evaluate the safety and effectiveness of a device on post-refractive eyes. Should you vote for approval, such a condition attached to today's PMA would be a win-win for all concerned.

Second. Professional use information and patient information booklets. Preexisting dry eye should be listed as a contraindication warning in the professional use information and patient information booklets of any laser approved for LASIK brought before the FDA. The FDA's LASIK website has a section entitled "When is LASIK Not for Me?" Under the Other Risks section, it states, "Dry eye. LASIK surgery tends to aggravate this condition." Under another section entitled "What Are the Risks and How Can I Find the Right Doctor For Me?," it states, "Some people may develop severe dry eye syndrome. As a result of surgery, your eye may not be able to produce enough tears to keep the eye moist and comfortable. This condition may be permanent." This last slide shows that dry eye is a

significant factor of the 100 percent of LASIK patients that are reported in this survey.

We believe that the information published by the FDA with regard to lasers should be consistent with the information presented in laser device professional use information and patient information booklets. For the last approved LASIK device, dry eye syndrome was listed under exclusion criteria for the PMA study data. If dry eyes are excluded from PMA data, the same warning should be extended to the public.

The American Academy of Cataract and Refractive Surgery recently issued LASIK Screening Guidelines for Patients on June 4th, 2002. Under the less than ideal LASIK candidates listed have a history of dry eyes as they may find that the condition worsens following surgery. We recommend that these guidelines be consulted to update the information presented in both professional use information and patient information booklets.

A similar argument can be made with regard to the issue of pupil size. In any professional use information and patient information booklets that we have read for this same laser device, the language is not consistent. By way of example, with regard to the last FDA-approved laser, it states in the professional use information that visual performance could possibly be

worsened by large pupil sizes or decentered pupils. This sentence is not included in the Precautions Section of the patient information booklet. The FDA website under "When Is LASIK Not For Me?," states under Other Risk Factors, "Your doctor should screen you for the following conditions or indicators of risk: large pupils. Make sure this evaluation is done in a dark room." Jumping ahead a bit, "This can cause symptoms, such as glare, halos, starbursts, and ghost images, double vision after surgery. In some patients, these symptoms may be debilitating. For example, a patient may no longer be able to drive a car at night or in certain weather conditions, such as fog."

The overriding point is that the information put forth by the FDA on its website and what it requires of manufacturers in professional use information and patient information booklets should be consistent with regard to dry eye, pupil size, and any other pre- or postoperative information provided to the public. Degree of success for higher myopes being yet just another example.

Also, we suggest that pictures be provided in patient information booklets so that patients understand the visual manifestations of both lower and higher-order aberrations in various lighting conditions, particularly at night.

And lastly, post-approval studies. If required

for contact lenses, by way of example PMA for the CIBA Extended Wear Contact Lens, it is logical to expect that the same for LASIK, PRK, LASIK, or any other laser device used to perform these surgeries. Lastly, questionnaires should be included to account for any potential adverse effects on quality of life.

Surgical Eyes is cautiously optimistic that post-refractive patients with complications may indeed benefit from controlled studies of the wavefront device being presented here today. We support such advancement. No less important is the identification and ready disclosure of all pre- and postoperative risk factors to patients and doctors alike.

Members of the panel and the audience, thank you for your time.

DR. WEISS: Thank you very much, Mr. Link, for your thoughtful comments.

I'd ask the panel at this point if anyone has any questions for Mr. Link. Dr. Bullimore?

DR. BULLIMORE: This is Mark Bullimore. I have a question for the FDA.

The PMA does not cover therapeutic use of the device. It just covers primary LASIK, is that correct? I'd like to add my thanks to the chair's. I do appreciate your efforts at advocacy.

MR. LINK: Thank you.

DR. WEISS: Dr. Bradley?

DR. BRADLEY: Question for the speaker.

You are suggesting that the FDA mandate a one-month follow-up post-surgical clinical study.

MR. LINK: On post-refractive eyes, yes.

DR. BRADLEY: Are you aware that those that we're studying today has one-month, three-month, and six-month, and that's typically what we see? I'm wondering. Are you suggesting something different from that?

MR. LINK: Well, I think from the anecdotal reports that we've heard of global wavefront treatment, the results, the efficaciousness of the procedure, is noticed immediately. So at a one-month period, from the doctors that I've spoken to who've done the procedures, say that you do see whether or not it's going to work. For instance, on a decentered ablation or spherical aberrations. What we want to avoid is people rushing to have it done and then there not being the necessary controls to see if it actually works, and if the FDA were to vote for approval with conditions, we would have data that could be shared openly and I think it would be a good thing for all of us.

DR. WEISS: If there are no other questions, thank you, Mr. Link.

MR. LINK: Thank you.

MR. WHIPPLE: Jayne?

DR. WEISS: Yes, Dr. Whipple?

MR. WHIPPLE: Very quickly, for Mr. Link.

MR. LINK: Yes.

MR. WHIPPLE: You've recommended some specific changes to the website for updates on our FDA website.

MR. LINK: Well, I think by virtue of the fact that the patient information booklets and the professional use information, it's my understanding that what is present there is mandated by the FDA, and the patient information booklets are to end up in the hands of the patients. The information that is on the FDA website is actually more stringent than what goes in the patient information booklets, and we believe it should be consistent throughout all three forums.

MR. WHIPPLE: Periodically, obviously, we update our website and we'll take into consideration what you've said and see if there's any merit to making any changes.

MR. LINK: Yes. If the information that's on the site ends up in the booklets and the professional use information, that would be superb.

MR. WHIPPLE: Thank you.

MR. LINK: Thank you.

DR. WEISS: Thank you very much.

We have a letter from an additional person who was not able to appear here today that Sarah Thornton will read to us.

MS. THORNTON: "Dear FDA Panel Members: Unfortunately I was not able to attend today's meeting in person. However, I would like to request that this letter be read aloud on my behalf.

"Two years ago, I had LASIK surgery. My initial uncorrected visual acuity was 20/50, 20/20. I was therefore considered a LASIK success. The reality is that as a result of having large pupils, I have debilitating loss of night vision, ghosting, haloes, starbursts and loss of contrast sensitivity. My eyes are extremely dry and burn constantly. Over time, I experienced a loss of approximately 35 percent of the surgical effect. Rigid gas permeable contact lenses are my best hope for visual rehabilitation. Unfortunately, I am intolerant to hard lenses, probably due to my dry eyes.

"I wish I could describe to you the totality of what LASIK surgery has done to my life. Driving at night is extremely difficult and dangerous for me. I can no longer enjoy things that I used to take for granted, such as going to the movies or dining in a dimly-lit restaurant. Now, I see two or three smeared moons in the sky at night.

"Today, you will be considering an application for wavefront customized LASIK. I completely support the advancement of this technology that has the potential to treat post-surgical eyes for the correction of induced higher-order aberrations such as those I suffer from.

"More importantly, however, I am asking the panel to condition this PMA approval to include preexisting dry eyes in the contraindications and to limit the approval of this device based on pupil size. The scoptic pupil measurement should not exceed the effective optical zone. The transition zone is not receiving the full refractive treatment and therefore should not be included as part of the optical zone for this purpose.

"Wavefront custom ablation is still LASIK surgery. In the words of Dr. I. Howard Fine, past President of the American Society of Cataract and Refractive Surgery, 'As we all know, LASIK transects the corneal nerves, therefore inducing dry eyes in most patients.' The size of the optical zone in wavefront treatments is limited, just as in traditional LASIK, by corneal thickness. Limiting the optical zone results in the induction of spherical aberrations in patients whose pupils dilate larger than the optical zone in low light. On Table 16 in the Summary of Safety and Effectiveness Data for the approval of the LADARVision laser, 29.5 percent of

the patients in the study reported halos that were worse or significantly worse postoperatively. I believe these patients reporting worse halos were primarily the patients with large pupils.

"I know another woman with 8mm pupils who was treated on the LADARVision system by one of the investigators for this PMA. She, too, sees massive starbursts and halos at night, has dry eyes, regressed, and is battling recurrent corneal erosions. She struggles with uncomfortable hard contact lenses at times just to see her infant son's face clearly. The surgeon was fully aware of her large pupils before he treated her. Now, she is practically disabled at night.

"Patients are making their decision to have this surgery based on a barrage of advertising that doesn't disclose the risks or contraindications. My informed consent did not mention dry eyes or large pupils. Dr. Fine's statement shows that the industry is fully aware of the magnitude of the dry eye problem. Why is it not taking preventive action? The fact that 29.5 percent of patients were complaining of worse halos proves the industry does not even consider night vision problems as a complication, even though it can be incapacitating. This is a medically unnecessary, elective procedure and therefore should be held to higher standards.

"It is not enough to simply put warnings in the patient labeling. Surgeons do not always give patients a copy of the patient information booklet. I was not given one. To protect patients, the FDA must limit the device based on pupil size and dry eyes must be listed in the contraindications.

"Ladies and gentlemen on the panel, I believe that some good can come from my terrible experience. Please help me make a difference for future refractive surgery patients who don't know that dry eyes, glare and halos are not simply minor side effects. They are life-altering complications.

"Thank you very much."

DR. WEISS: Thank you, Sally.

We will also have Mr. David Shell approach the podium and he would also like to read a statement.

MR. SHELL: Members of the committee, I am David Shell, mechanical engineer from Arlington, Virginia. I appreciate the opportunity to speak here. The focus of my testimony will be on the inclusion of an incident of LASIK-induced dry eye statistic and to the patient information booklet for the medical device before us today.

Four years ago, I underwent LASIK. Since my surgery, I live in daily misery from burning and stinging eyes induced by LASIK. Artificial tears don't bring much

relief. Eyedrops give only temporary relief and cause greater visual distortion when used. My LASIK dry eye is not a minor problem, as downplayed by some ophthalmologists. It's a disability. I estimate that I am blind approximately 10 percent of the time due to my eyes being closed because of the pain. At the time of my surgery, I was told only a small number of patients experience a complication from this procedure.

There is substantial evidence that shows this crippling side effect to be relatively common. For example, an article in EyeWorld stated that 100 percent of patients have dry eye after LASIK. While most patients improve, many do not. Numerous articles in industry magazines and journals talk about how to manage LASIK dry eye. Internet websites, such as www.surgicaleyes.org, discuss this issue frequently.

I know now that I did not have the information that would have assisted me in making a fully informed decision. No one really knows the risk of getting this debilitating condition in terms of percentage or the information is just not getting out. Therefore, a person is unable to make an informed decision about having this procedure. Should not this type of data be available to the public? This type of data is no where to be found in the patient information booklet.

My recommendations are as follows. Premarket approval for this medical device should be contingent upon manufacturer conducting clinical studies on the incident of LASIK-induced dry eye; data to be listed in the manufacturer's patient information booklet in terms of percentage, not just a casual mention that one could get dry eyes from this procedure. We need a percentage.

Adoption of these recommendations will help increase public awareness about this serious overlooked complication. I believe these recommendations are fair and reasonable, easy to administer, and do not impose an undue burden on the industry.

Before I conclude, I want to remind everyone that our eyes are very precious. The standards for safety and effectiveness need to be very high for an elective procedure on one's eyes. Personally, I don't think they're high enough. I didn't need this surgery and ended up with inheriting a lifetime of misery and pain. I'm asking the committee to make certain that any device that purports to correct a relatively minor problem does not create crippling visual defects as a result.

Members of the committee, this concludes my testimony. Thank you very much.

Also, I'd like to add, if anyone wants to try some Dry Eyes, during the break, I have a number of unused

vials up here, and I'd be happy to give you one.

DR. WEISS: Thank you.

Does anyone have any questions for Mr. Shell?

(No response.)

DR. WEISS: Seeing no questions, thank you very much, Mr. Shell.

Are there any other participants who would like to come forward during the open public hearing?

(No response.)

DR. WEISS: If not, that will end the open public hearing, and we will move on to the open committee session and start with the FDA division update.

Dr. Whipple?

MR. WHIPPLE: Thank you. It's Mr. Whipple, by the way. Thank you for the promotion.

It's been some time since I've had a chance to address this panel. I'm usually doing my thing behind the scenes and occasionally going up to Ralph after the meeting or during the meeting and whispering things in his ear, that kind of thing. But Ralph can't be with us today and he's asked me to set in for him and I'm glad to do that. He does send his regards to everybody here and he wants to make sure you know that he will be at the next panel meeting.

Now, as for division updates, the branch chiefs

really have all the important information to provide to you, so I won't steal their thunder or step on their toes. But I do have one personnel piece of information that I do want to present. The office director for Device Evaluation, Dr. Bernie Statland, who is Ralph's boss, will be leaving the center at the end of August, and on behalf of the division, I want to thank Dr. Statland for his guidance and support in the past two years that he's been our office director. We sure will miss his kind and gentle demeanor and we do wish him well as he goes on to pursue a law degree at the University of Minnesota, and as soon as we know who Ralph's new boss is going to be, we'll let you know.

So that's all I have for now, and we can go on to the branch updates.

DR. WEISS: Thank you.

I think Dr. Saviola will be starting.

DR. SAVIOLA: Good morning, panel members.

I'd like to update you today on one 510(k) clearance and two PMA approvals. We recently cleared an application on May 9th, 20002, for the ChromaGen Reading Aid Soft Contact Lens manufactured by Cantor and Silver Limited of England. The indication includes the correction of refractive ametropia as it would for a standard contact lens. It also has a statement. "In addition, the lenses

may also be prescribed as a colored filter for individuals who experience reading discomfort not related to binocular vision problems or uncorrected refractive error."

This lens had previously obtained a marketing clearance in October of 2000 as an optical aid for people with red-green color deficiencies. There was a small clinical study conducted that supported the use of the lens as a colored filter to aid individuals who experience reading discomfort. The 510(k) Summary of Safety and Effectiveness available on our website provides a description of the clinical study, and for those interested, the K number is K012132.

Current literature studies report inconsistent results concerning the effect of colored filters on reading rate and comprehension and symptoms of reading discomfort, along with rate of reading and reading comprehension, can be strongly influenced by psychological factors. The clinical data in our view did not support the use of the ChromaGen lens in treating dyslexia or improving the general reading speed. Dyslexia is a poorly defined anomaly with some controversy as to how it is identified. Therefore, the lens is not cleared with the indication to treat dyslexia or improve reading speed and the precaution statement was added to the labeling to inform patients that results are variable due to the subjective nature of visual

discomfort and that not all patients will experience success.

In our view, there is minimal risk associated with this device as there's no indication to aid reading discomfort. The risk is comparable to other tinted soft contact lens and while effectiveness is expected to be variable, the lens may be beneficial for some people. We had issued a homework assignment to a panel member on this project, and I want to thank the panel for assistance in review of this submission.

The first PMA approval I want to inform the panel about is the Paragon CRT and Quadra RG Lenses for overnight orthocaratology which we discussed at the January 2002 panel meeting. These were approved on June 13th. Following the panel meeting, ODE issued an approvable letter which the firm responded to. Following review of the additional clinical data provided and interactive review of the draft product labeling, final review was granted. The lenses are manufactured by Paragon Vision Sciences of Mesa, Arizona, and the Paragon CRT designs are indicated for overnight wear in a corneal refractive therapy fitting program for the temporary reduction of myopia up to six diopters in eyes with astigmatism of up to 1.75 diopters. The Paragon RG designs have essentially the same indications as the CRT lenses, except the pretreatment

of myopia is up to three diopters in eyes with astigmatism up to 1.5.

In order to address effectiveness concerns of the Quadra RG design used overnight, a further analysis of existing data was conducted by comparing the Quadra daily wear effectiveness data with the CRT overnight data for a three-month time interval which was the duration of the data we were studying. There are no statistically significant differences in reduction of pretreatment refractive error, accuracy stability or uncorrected visual acuity.

As to the age issue that was discussed during the panel meeting, among the many recommendations by the advisory panel was the limitation to those 18 years of age or older since limited data on this age group were presented during the panel meeting. There was not an age restriction included in the final approval by FDA since the company provided additional data on adolescents between ages 12 to 17 who completed the study, and they accounted for 11 percent of the completed dataset.

The primary effectiveness concern for this age group is their expected progression of myopia. Although daily wear contact lens wear can reshape the cornea or known as orthokeratology has been practiced since the 1960s, the long-term safety effects of overnight wear for

reshaping the cornea are not known for any age population and there's not been shown any real long-term safety issues for daily wear orthokeratology.

And the last PMA update is for the Menicon Z, which is an RGP lens, that was just approved in July, on July 12th, 2002, and this is a supplement for P990018 for extended wear of an RGP up to 30 days of wear. This had a prior daily wear approval in a variety of designs for indications for myopia, hyperopia and presbyopia in both aphakic and non-aphakic persons. In the extended wear version, it's approved in the spherical, aspheric and non-prism ballast toric and non-prism ballast multifocal lenses for again myopia, hyperopia and presbyopia, but it's only for non-aphakic persons, and there's limitation on the power range of up to +8 diopters for hyperopes.

Although this was not discussed at a panel meeting, we did solicit homework assignments from three panel members in order to corroborate the internal FDA clinical review. The panel reviews did not raise any additional clinical issues that were unique to this device or different from those identified in the internal review. All three homework assignments recommended approval of the device for extended wear up to 30 days. The post-approval condition of conducting a clinical study was placed upon this approval in the same manner as the previous two

silicone hydrogel lenses from CIBA and from Bausch & Lomb.

That concludes my remarks. Does anybody have any questions?

(No response.)

DR. WEISS: Thank you, Dr. Saviola.

Dr. Lochner will update us.

MS. LOCHNER: Again, thank you for that honorary medical degree.

DR. WEISS: I'm giving out medical degrees left and right here today. Step right up, Ms. Lochner.

MS. LOCHNER: All right. At the January 2002 meeting, the panel reviewed P010059, the Morcher capsular tension ring, and recommended that the PMA was approvable pending additional analyses of the clinical data. I would like to advise you that this document is still being reviewed by FDA. The issues that the panel discussed were related in a letter to the sponsor and we are currently awaiting their responses.

Secondly, I'd like to advise you that on March 26th, 2002, we cleared a new glaucoma shunt from Optonol, Limited, K012852, the Ex-Press Miniature Glaucoma Implant, Models R-30 and R-50, and this device is different from previously cleared shunts in that it is a stainless steel tube with a blunt needle-shaped penetrating tip at one end and a flat angled flange at the distal end. It functions

similarly in shunting aqueous fluid from the anterior chamber into a conjunctival bleb and is intended to reduce intraocular pressure in patients with glaucoma where medical and conventional surgical treatments have failed.

That concludes my comments.

DR. WEISS: Thank you.

Are there any questions?

(No response.)

DR. WEISS: Thank you.

We'll go on to Dr. Beers.

DR. BEERS: Thank you.

We've approved three devices since the last panel. A couple of months ago, we approved the Bausch & Lomb PMA P990027 Supplement 2 for the Technolas 217A for high myopia and that's up to MRSC of less than -12 with a sphere of less than 11. We also on April 11th, 2002, were approved the Refractec PMA, P010018, for the ViewPoint CK or Conductive Keratoplasty System. That was reviewed by this panel which recommended that it was approvable on November 30th of 2001.

Based on the panel's recommendations, the indication for this device is for the temporary reduction of spherical hyperopia in patients who have .75 diopters to 3.25 diopters of psychoplegic spherical hyperopia, and also added to the indications for use is the statement that the

magnitude of correction with this treatment diminishes over time in some patients, with some patients retaining some or all of their intended refractive correction.

The other device that we approved was approved on December 19th, 2002, for the VISX Humanitarian Device Exemption, or HDE, H000002 for the Customized Contoured Ablation Pattern Method for the treatment of certain patients, and the indication is important here, for the treatment of certain patients with symptomatic decentered ablations from previous laser surgery as viewed on the Zeiss Humphrey topography unit.

Now, I'm guessing that many of you don't know what an HDE is. An HDE is an application that's similar to a PMA but is exempt from the effectiveness requirements of PMA. An approved HDE authorizes marketing of a humanitarian use device. The humanitarian use device is intended to benefit patients in the treatment and diagnosis of diseases or conditions that affect fewer than 4,000 individuals per year in the U.S. So obviously given such a small patient base, it's difficult for these types of devices to gain significant clinical trials to support safety and effectiveness or certainly to support the effectiveness. So this is a little bit different route for some of these.

It's important, though, to remember with these

devices that the use of the device at each institution is overseen by the IRB of that institution and the IRB may make decisions on whether to use the device on a case-by-case basis. So there are certain severe -- well, I wouldn't say severe but there are certain limitations on the HDE that you don't see with a PMA.

That concludes my presentation. Are there any questions?

DR. WEISS: Dr. Bullimore?

DR. BULLIMORE: Mark Bullimore. I have a question for Dr. Beers. It is Dr. Beers.

You say the approval is limited to 4,000 cases per year. Is that the actual approval or is that just --

DR. BEERS: That's in the Act. I mean, that's a limit.

DR. BULLIMORE: The FDA has no role or responsibility to monitor the number of procedures that are done after approval?

DR. BEERS: They are monitored. The sponsor has to keep track of that.

DR. BULLIMORE: Okay. Thank you.

DR. WEISS: If there are no other questions, I'd like to thank Dr. Saviola, Ms. Lochner and Dr. Beers.

If there's no other information to be updated from the agency at this point, we're going to move ahead to

the discussion and review of PMA Number P970043/S010.

I passed muster with Sally, so I must be doing okay.

We'd like to inform the sponsor they have one hour, and I would like each presenter when they come forward to identify themselves at the beginning of the presentation, also to inform us of any financial conflicts or potential conflicts.

MS. CHESTER: Good morning. I'm Kathleen Chester, Director of Regulatory Affairs for Alcon's Refractive Products, and today, we'll be presenting the clinical results from the CustomCornea Myopic LASIK Clinical Trial involving the commercially available LADARVision Laser System.

The agenda for our presentation includes the following: I will give a brief introduction. Dr. George Pettit from Alcon will provide an overview of wavefront technology. Drs. Daniel Durrie and Omar Hakim, two of our clinical investigators, will present a summary of our safety and effectiveness results. Dr. Pettit will then discuss our wavefront aberration clinical outcomes followed by Dr. Stephen Brint who will discuss the clinical implications of wavefront correction based on our clinical results. And finally, if time permits, we will respond to a number of questions we received in advance from the

panel.

This PMA supplement application requests an expansion of the existing indications to include wavefront-guided custom cornea LASIK correction of myopia of up to -7 diopters of sphere and less than -.5 diopters of cylinder at the spectacle plane in the subjects who are 21 years of age or older and with a documented stability of refraction.

Alcon is pursuing approval of spherical myopia only at this time. There are no safety issues related to this decision. The decision is based on the intent to provide the most effective astigmatic outcomes possible with this new technology with minor adjustments in the algorithm before seeking approval for the myopic astigmatism indication.

The study population consists of a safety cohort of 426 eyes in the range of up to -7 diopters of sphere and up to -4 diopters of astigmatism. The primary effectiveness cohort is comprised of a subset of those eyes, of which there are 139, in the range of up to -7 diopters of sphere and less than .5 diopters astigmatism.

Now, I'd like to introduce Dr. George Pettit who will give you an overview of wavefront technology.

DR. PETTIT: Good morning. I'm the chief scientist at the Alcon Orlando Technology Center and therefore I do have a financial interest in this

technology.

I'd like to start with a very simple introduction to what is wavefront-guided ablation. What are we talking about here? When we talk about wavefront-guided customized treatment, our definition includes, first, a quantitative measurement of both the lower and higher-order aberrations -- i.e., those aberrations beyond simple sphere and cylinder -- that are present in the eye and transfer of that detailed aberration data to an excimer laser which positions the treatment profile correctly on the eye and calculates and delivers a specific ablation pattern unique to each patient based on the preop aberrations. So it's important to note that the ablation pattern is unique and is based on the preop aberration measurement for each eye.

DR. WEISS: Dr. Bullimore, you're obscuring the view.

DR. BULLIMORE: I apologize.

DR. PETTIT: So the technology requirements in order to effect this type of treatment, there's two components. First, we have to have a wavefront system that's capable of measuring the higher-order aberrations obviously accurately, quantifying the wavefront aberrations in the patient, and we also need the wavefront device to accurately register where exactly on the eye those

wavefront aberrations came from.

The treatment laser we use employs an active high-tracking system to stabilize the eye during the surgery, compensate for patient eye movement, and allow us to deliver the customized ablation profile as accurately as we can. We use a small Gaussian excimer beam to precisely scope the subtle contours in the corneal surface and we use fairly sophisticated software algorithms to convert the wavefront data into the appropriate treatment profile.

So what is wavefront sensing? I'd like to give just a very simple introduction so we all know what we're talking about here. Simply put, wavefront sensing is a measurement of how the eye operates as a integrated optical system, and the wavefront device gives you a detailed refractive map over the pupil of the eye. We think in simple terms of how a theoretical perfect eye sees the world. When a simple perfect eye looks at a far-off target, the light from each point in that target enters the eye as a bundle of parallel rays. The wavefront is the surface perpendicular to each of those rays. So in the case of a perfect eye, the wavefront entering the eye from a distant target is a flat wavefront and that flat wavefront is well focused down to a very small spot back on the fovea.

Now, in the case of myopia, which is the

indication we're considering this morning, when a myope looks at a distant object, those parallel light rays are not well focused on the retina. They're focused somewhere in front of the retina, but by the time the light reaches the retina, they're blurred out. A myope can see clearly if the target is up close to the eye. So you imagine a nearby point source, the light rays from that nearby source enter the eye as a diverging bundle. The wavefront in that case is part of a spherical surface and that spherical wavefront is then well focused down to a small spot on the retina.

When we perform classical vision testing, we're in a sense doing a primitive form of wavefront sensing. We're asking what combination of spherocylindrical lenses do we need to put in front of the eye so that that flat wavefront from a distant source is as best focused as possible back on the retina? The limitation of that, of course, is that there are higher-order aberrations that are known to exist in the eye and these cannot be characterized with simple spherocylindrical lenses. This is an example of spherical aberration whereby the periphery of the eye is more refracting, has more myopic power than the central part, and the rays are blurred out in the retina. Another common example is coma and coma can be simply thought of as one side of the pupil being slightly more myopic than the

average and the other side being more hyperopic than the average. Again, it causes blurring, puts the light back on the retina, and this can't be characterized well with simple lenses.

When we perform wavefront sensing using the Shack-Hartmann approach, we take advantage of the fact that light is reversible. If we want to study how light gets from Point A to Point B, being refracted at various surfaces within the eye, we can instead measure how light travels from Point B back to Point A. So what we do is we have the patient look into the device and then we shine a narrow eyesafe probe beam into the eye and illuminate a small patch back on the fovea. Some of that light is scattered back out of the eye just like when you do flash photography and you get a red eye effect and outside the eye, we now have a reemitted wavefront which is just the time-reverse process of how the myopic patient sees the world. So now we have that same spherical surface but it's traveling out of the eye rather than into it.

So how do we measure what that wavefront looks like? Well ,inside our wavefront sensing device, there's a group of relay optics, so that this plane over here is imaged over here right at the entrance space of the actual wavefront sensor. So whatever the wavefront is doing as it exits the eye, it does again over here at the wavefront

sensor itself. Now, let's zoom in on the wavefront sensor. This slide shows a simple myopic wavefront impinging on the wavefront sensor itself and I've isolated one lens lit up here. You're seeing part of the wavefront go through that lens lit. There's an array of microlenses with a CCD camera screen sitting at a fixed distance behind it and through one of those lenslets, this piece of the wavefront is being focused to this camera screen at this point here.

Now, if the wavefront was perfectly flat, that light would have traveled straight through and then hit the screen over here. We want to measure or actually describe what the wavefront looks like in some mathematical term, W of X and Y, where X and Y are the transverse pupil coordinates, and let's consider that single lenslet sitting at the location of Y not. We know that the wavefront piece that went through that lenslet traveled this distance to get back to the CCD camera and it's laterally displayed from its ideal location by delta Y. From that information, we can calculate the slope of the incident wavefront at that lenslet and by doing this at a large number of points across this lenslet array, we're actually able to rebuild the shape of the original wavefront.

This is an example of the CCD camera screen showing you a picture of the focused light dots. The software in the wavefront device goes in and finds the

centers of all those dots, figures out how they're related to one another, and more importantly which lenslet each one of them came through them, and from this picture and the processing of the information, we calculate the shape of the original wavefront.

Now, we have to have a set of mathematical tools to describe what does the wavefront look like. It's going to be a complicated surface and we need to describe it. We use what's called Zernike polynomials, which are a convenient mathematical basis set for describing visual aberrations. There's an infinite number of these. They come in orders which are shown by the different layers in this pyramid. So there's an infinite number of these going off to the bottom there and you can see as you work your way down the pyramid, the orders become progressively higher and the shapes become progressively more complex. These second-level, second order aberrations are closely associated with the conventional spherocylindrical errors in the eye, and then the higher-order aberrations correspond to the lower layers in that pyramid.

Now, from the wavefront information, we can estimate the optical performance of the eye. We can take the wavefront and calculate what's called the point spread function which is an optical analysis of what a distant point source would look like on the retina. So in the case

of a perfectly flat wavefront over a big pupil, that wavefront is focused on the very tight spot, and this is a simulated optical image of what the retinal image should look like when the patient looks at approximately 20/16 through through 20/10 lines on an eye chart. They're slightly blurred out due to the effects of defraction, but this is about as well as the optics can do for a 6.5mm pupil.

I'll just show you a couple more examples. This is myopia, that simple spherical shape. The way to think about it, the wavefront of the eye is down here and the wavefront's propagating up out of the eye. Myopia causes, as you can see, blurring of the optical image on the retina. I should point out that this does not take into account retinal effects or neuroprocessing. We don't know exactly how well an eye cognitively could see the eye chart, but this is a simulation of what the optics of the eye produce on the retina.

I'll just show you one more. This is vertical coma, and you can see that in this case, you actually can read all these letters, but there's this sort of comet-like tail extending in the downward direction due to the coma present in the eye.

In addition to being able to provide a detailed mathematical description, we also want to have a simple

single parameter to characterize, well, just how distorted is this wavefront? So, we use what's called the RMS error. You can hear this mentioned several times this morning. The RMS error is simply the standard deviation of the wavefront relative to that idealized flat profile. So, if the wavefront is in fact perfectly flat, the RMS error is going to be zero, and as the wavefront becomes more and more distorted, the RMS error becomes progressively more positive. That's a very simple overview of wavefront sensing, and there's a lot of details that I simply don't have time to go into in this one hour.

So in a clinical wavefront sense, we need a little bit more equipment to actually be able to measure a patient accurately, and so this slide shows the principle optical components in our wavefront-sensing device. The eye is sitting here looking into the instrument. We obviously have to give the patient a target so they know where to look, and these are myopic patients, so they don't see very well before surgery. So our target has an adjustable focus mechanism to correct for the preoperative myopia and actually to fog the eye slightly to try to minimize any accommodation effect as the patient looks in there.

We have a video camera that's staring out at the eye that helps us position the eye for the measurement

and equally important, it helps us record exactly how the eye was positioned and how it was rotated at the instant that the wavefront data was taken. We've already talked about the probe beam and the wavefront-sensing pathways.

So how do we perform a surgical wavefront measurement? When a patient comes into the clinic on the day of surgery, the first thing that actually happens before they have any dilation applied to the eye is we have them sit down at the wavefront sensor and we take a video snapshot, so they look into the device and we use that video path to capture a frozen picture of their eye under daytime illumination conditions, and we do this because we want to record where their daytime natural pupil center sits relative to their limbus. We do this by asking the clinician to align two software reticles in the frozen video image, one to the limbus and one to the pupil, and having done this, our software now knows where the daytime pupil center is relative to the limbus and that's going to be our anchor point later on.

The patient then goes off and has the eye dilated and in this trial, we used a combination of tropicamide and phenylephrine. Immediately before the wavefront measurement, the surgeon applies two ink marks using a standard eye-marking pen to the sclera just outside the limbus. The patient then sits down at the wavefront

sensor. They're positioned appropriately. They view the target. We fog the eye, and then we take five repeat wavefront measurements in relatively quick succession. At the instant that each of those wavefront measurements is taken, the video image is frozen. So we have a frozen video image that's synchronized with the wavefront capture, and we ask the technician in that frozen image to align two reticles, one to the limbus, so that's an elliptical reticle, and we also have a linear reticle that they're supposed to draw through these applied ink marks, and with this information and the wavefront data, we now know exactly where the wavefront came from on the eye and the cyclotorsional angle of the eye at the measurement time.

The five measurements are then automatically analyzed and the two outliers are rejected based on a statistical analysis of the RMS errors. The remaining three are then compared for consistency and then averaged together to make a final composition wavefront and this is what we actually base the surgery on. As a final sort of sanity check, we can back calculate the effect of clinical prescription from the wavefront data and compare that to what was measured at the foropter, and in this trial, it's worth noting that we require both the sphere and cylinder calculated from the wavefront had to agree within 1 diopter with what was measured at the foropter.

The wavefront and the geometry information are then transferred electronically to the treatment laser. Our treatment device again employs a blind spot, relatively small, 193mm excimer laser, uses an active eye-tracking system to stabilize the eye during the treatment, and it's currently approved for all conventional treatment types of refractive error.

The LADARVision treatment device actually takes the wavefront data and calculates the appropriate ablation profile. The patient lies down, is prepared for the surgery, and in the tracked image, once the patient and the doctor are ready, in the tracked image of the eye, a single linked reticle, a combination of the elliptical limbus reticle and the linear cyclotorsional reticle, comes up in the tracked image screen and the clinician then aligns these to the anatomical features on the eye and that's how we register the ablation profile correctly both in position and cyclotorsional angle.

The device requirements on the wavefront-sensing unit itself then. First, it must record the natural pupil limbus geometry. It must measure wavefronts up to at least the fourth Zernike order which is what we used in this study, must be able to measure pupils in excess of 7mm in diameter, obviously has to have a validated accuracy in wavefront measurement performance,

must record the geometry of the wavefront data relative to the limbus and the cyclotorsion features, these are these applied ink marks that I referred to, and it must be able to obviously export the wavefront and the geometry data in a format compatible with the LADARVision system.

I'd now like to turn the podium over to Dr. Dan Durrie who's going to summarize our safety data.

DR. DURRIE: Thank you very much.

It's a pleasure being here, and I'm Dan Durrie, and I'm one of the investigators in this clinical trial, and I'm a consultant for Alcon and I'm also a paid consultant for a competing technology.

I'd like to review the safety criteria of this particular study that's under question. First, I'd like to clarify a little bit of the two groups that we'll be talking about. The safety cohort includes 426 eyes which includes the astigmatism cases that we're not asking for approval for today but are included in the whole safety cohort. The primary efficacy cohort as has been shown before is 139 eyes and were the ones without significant astigmatism. This is based off the manifest refraction, and as I go through this, I'll be showing any differences.

First, accountability is always important with any clinical trial and this was excellent. It's always great to see a 100 percent down at the bottom of the

accountability chart. Unfortunately, there were two eyes that were lost because of the death of a patient to colon cancer, but it was a 100 percent of all patients who were available were accountable at all visits. So therefore, we can have at every visit 139 eyes in the spherical cohort and in the safety cohort of all the eyes is all the eyes available except the two that were lost at the six-month visit.

As far as the demographics, and I will compare the two groups, they are very similar. Between the two groups, the points of interest are the fact that this was primarily a male study and as with most excimer laser studies, it's predominantly Caucasian and also we note that most of these patients were soft contact lens wearers. The age was in the upper 30s and similar between the two groups. Also as far as the amount of correction that was attempted, the only difference between the two groups really was the fact that there was the spherical group did not have the cylinder as previously described but other than that, the average amount of myopia and the range was similar in the two groups.

Now, again, I'm going to talk about safety and this is the total group with a 100 percent follow-up of those available. We're all familiar with the guidance documents. We've reviewed these studies before, and if

you're using the criteria in the lines lost of best-corrected vision, we can see that this easily meets all the previously discussed guidelines. There was one eye that did have vision that was less than 20/25 that was 20/25 preop and the three eyes that had loss of two lines of best-corrected vision but no eyes that lost more than two lines.

Looking at the best-corrected data in a different way and overall lines lost or gained as a clinician, we like to see the graph leaning to this side from preop to postop which means that there is more lines gained than lost, and as you can see at the six-month follow-up, 37 percent gained one line or more and only 9.4 percent of patients lost any vision. For most studies, these are fairly even and now with these newer technologies, we're seeing the graph moving in that direction.

It also showed in looking at the best-corrected vision comparing preop to postop and looking at the high level of vision correction of 20/12.5, that we had a doubling of that in the study from preop to six-months postop and 20/16 increased from preop to postop. So the best-corrected vision overall was increased with this study.

In terms of complications and the way these are

reported, they're reported at any visit, any time. So that, the typical things we'd see with LASIK surgery, small amount of DLK, epithelial ingrowth, ghosting images, and some corneal edema, and there were other findings that were listed that were below the .2 rate that are listed at the bottom here. Nothing out of the ordinary here for a LASIK trial or LASIk clinical.

Now, what happened to those patients who reported complications? All but two eyes that had best-corrected vision of 20/20 or better and a 100 percent had 20/32 or better at the last visit. Also, all complications resolved, except for four eyes, and these were one patient with epithelial ingrowth and three patients with ghosting images. All the reported DLK and epithelial ingrowth were Grade 1 or less at all of the reporting visits.

In regards to adverse reactions, those related to the device, there was recalcitrant DLK associated with blepharitis in two eyes of one patient and there was one miscreated flap. The patient was exited from the study and had successful recut LASIK surgery with a conventional laser. There were also some unrelated to the procedure. There was one patient, I told you before, that died of colon cancer and one patient that developed multiple sclerosis during the procedure. There was one retinal horseshoe tear which was felt to be unrelated to the

procedure by the retinal specialist. What happened to those patients, of all those patients who had adverse reactions, a 100 percent of them were 20/16 or better at the last reported visit, and other than the multiple sclerosis, all of the other adverse reactions resolved. In regards to intraocular pressure, corneal haze or other slit lamp findings, there was nothing unusual in this study and there was nothing that was out of the ordinary that we would expect. So the overall safety of this study was extremely good.

Going to the spherical cohort, this is 139 eyes, just quickly showing you that if we look at that group, there was all zeroes on the parameters for the FDA guidance and no eyes had worse than 20/20 vision. In regard to complications, it's the same distribution but slightly less in this group, and there was no adverse reactions in the spherical myopia group that we'll be discussing for efficacy.

Therefore, the safety criteria in this study meets or exceeds the guidelines for loss of best-corrected vision, best-corrected vision worse than 20/40 and induced cylinder and the incidence of adverse reactions were overall, and there was no demonstrated significant safety concerns.

I'd like to introduce Dr. Omar Hakim who will

be talking about efficacy and this again to define is 139 eyes that are in the efficacy group.

Thank you.

DR. HAKIM: Thanks, Dan.

Hi. My name is Dr. Omar Hakim. I'm Medical Director for TLC Laser Eye Centers in Canada. I've been performing laser refractive surgery since 1994 and custom ablation surgery since May of 2000, using a variety of different platforms, and actually I had my own vision corrected with LASIK in 1998. I am a consultant on Alcon's Refractive Medical Advisory Board and travel expenses for this meeting were paid for by Alcon.

I've been asked to present the effectiveness outcomes for the 139 eyes in the study. Preoperably, these 139 eyes had up to 7 diopters of myopia and less than half the diopter of astigmatism. First, we'll review the manifest refraction spherical equivalent results and we'll see that following surgery here on the left, that 83.5 percent of the eyes had an MRSE within half a diopter of emmetropia at one-month postop and 74.8 percent at six months following surgery. Fully 97.1 percent of the eyes were within 1 diopter of emmetropia at one month and almost 96 percent at six months. Both of these groups clearly exceed the FDA Guidance Document guidelines calling for 50 percent of patients to be within half the diopter of

emmetropia and 75 percent within 1 diopter of emmetropia.

This graph shows the attempted versus achieved correction at six months of all 139 eyes and it really demonstrates the vast majority of eyes fall within a 1 diopter bracket on each side of emmetropia shown by the dashed line here. At the higher ranges of correction, there are three eyes that fall outside the 1 diopter bracket. However, even at these higher levels of myopia, excellent results were still reported with uncorrected visual acuity of 20/25 or better in 92 percent of the eyes between 5 and 5.99 diopters and 75 percent of the eyes above 6 diopters or above. In fact, in this higher myopic group, 75 percent of the eyes were still within half a diopter of emmetropia. However, overall, there was a small amount of undercorrection as shown by this slide. When we reexamined the results around this mean MRSE line of -0.37 diopters, we see that actually more than 90 percent of eyes were within half a diopter of this mean value, reflecting really a very high level of precision and reproducibility of result.

This chart looks at the MRSE over time and shows excellent stability from one-month postop with refractive MRSE of -0.27 diopters, -0.35 at three months, and -0.37 diopters at six months. Again, the notable precision of the MRSE is shown in the standard deviation

values which range from 0.34 diopters to 0.42 diopters of standard deviation. Of course, surgeons routinely make adjustments in treatment based on environmental factors, such as temperature and humidity, and surgeon-specific or site-specific factors because we know these influence the accuracy of our outcome in every-day surgery. The accuracy of these results reflected in the fact that we had a mean undercorrection of -0.37 diopters were limited by the study protocol because it restricted clinicians from making these usual treatment adjustments. This undercorrection could be dealt with by usual nomogram, adjustments by the surgeon or could be incorporated into the software and as commented on by Dr. Eydelman in her medical officer's review, Alcon has already initiated a clinical evaluation of the minor software adjustment to address this.

In terms of stability of MRSE, then we see that 100 percent of eyes between the one- and three-month visits and three- and six-month visits had less than 1 diopter change in MRSE, surpassing the FDA Guidance Document guidelines. In fact, the mean change was only .07 diopters in the one-to-three-month period and -0.3 diopters in the three-to-six-month period, which translates into a mean change per month of -0.035 diopters and in the three-to-six-month group of -0.01 diopters, really incredibly good stability.

This chart then shows the percentage of eyes achieving uncorrected visual acuities of 20/20 on this side and 20/40 on the right side. We see that 86.3 percent of eyes at one month had 20/20 uncorrected acuity and 79.9 percent at six months had 20/20 acuity. Looking at 20/40, we see that 99.3 percent of eyes had that acuity level at one month and 98.6 percent, almost 99 percent, at the six-month visit. Again, these results exceed the FDA guidance calling for 85 percent of eyes to have uncorrected acuity of 20/40 or greater.

It really should be noted that these excellent uncorrected acuity results were obtained despite the mean undercorrection of -0.37 diopters that we noted previously and a reduction in this undercorrection along with the excellent precision of effect as shown by the MRSE results should provide even better uncorrected visual acuity results with nomogram adjustment, and in fact, at one month, 59 percent of eyes had uncorrected visual acuity equal to or better than their preoperative best spectacle-corrected acuity and at six months, this figure was still 52.5 percent.

In summary then, this study of CustomCornea Wavefront-Guided Ablation has demonstrated uncorrected visual acuity results and accuracy and stability of MRSE results that exceed those called for by the FDA Guidance

Document. Patients were also asked to grade any ocular or visual symptoms. With regards to ocular symptoms, only 2.2 percent of patients noted significantly worse dryness of their eyes and only 1.5 percent noted significantly worse burning or gritty sensation with their eyes at six-month postoperatively, and in fact, many patients actually noted they had significant decreases in symptoms, including significant, for example, you look at dryness, 8.1 percent of patients said their dryness of their eyes was actually significantly better following surgery.

On evaluation of the visual symptoms, 2.9 percent of patients noted they had significantly worse blurring of vision and 0.7 percent of patients noted they had significantly worse night driving difficulty, double vision or fluctuation of vision. What's interesting is that if we looked at the mean MRSE on patients who said they were better or significantly better, that ranged from .26 diopters to -0.36 diopters, and in the group who noted that their symptoms were worse or significantly worse, that range was -0.46 to -0.7 diopters. So that, again, further improvements in undercorrection may further improve upon this already-low level of symptoms.

As a surgeon, all these visual symptoms are important, but the most concerning to me, you know, really the top three, glare, halos, and night driving

difficulties, and, you know, here we see that although the numbers are small, more patients actually said their symptoms were significantly better than significantly worse following surgery.

At three months following surgery then, 85 percent of patients said that they were satisfied or extremely satisfied overall and at six months, this was 79 percent. Again, the MRSE in patients who were satisfied or extremely satisfied was -0.3 diopters and in the unsatisfied or extremely unsatisfied group, that was -0.93 diopters, and again a reduction in this undercorrection should shift the cohort towards even higher patient satisfaction rates. Almost 90 percent of patients described their quality of their vision as being equal, better or significantly better following surgery at both the three- and six-month intervals, and over 95 percent of patients at three months and 94 percent of patients at six months had no need for distance correction of any kind.

So again, in summary, the study of CustomCornea Wavefront-Guided Treatment has clearly exceeded the performance guidelines laid out in the FDA Guidance Document in terms of uncorrected visual acuity and accuracy and stability of postoperative manifest refractive outcome.

Dr. George Pettit's now going to return and discuss the wavefront and higher-order aberration outcomes

for the cohort.

Thanks, George.

DR. PETTIT: Now we're going to talk about the higher-order aberration changes that we saw in this myopic cohort.

This slide summarizes the changes in the various higher-order parameters. So the third- and fourth-order aberrations are considered along the horizontal axis here. We're looking at the total higher-order aberration content and then the individual content from the various third- and fourth-order aberrations. The vertical axis indicates the magnitude of the different wavefront parameters. The blue bar indicates what they were preoperatively, so that's the starting baseline level, and then the green, yellow, and red bars indicate the one-, three- and six-month postop measurements on this cohort.

Now, I'd like to just note there's 137 patients in this table. The entire cohort was 139 eyes, but there were two eyes that missed one of these wavefront measures at some interval. So, there's 137 eyes considered here and that's why the N is slightly smaller. The little asterisks indicate those changes that were statistically significant between the preop and the six-month postop interval and you can see that for almost all of the aberration parameters, they're actually slightly higher by a statistically

significant amount after surgery than before. The trifoil is actually less after treatment but it's not a statistically significant difference.

Now, I should just also mention this is based on a 6.5mm wavefront analysis diameter. This isn't a surprising finding. It's well known that LASIK tends to increase the higher-order aberrations. So an important question to ask is how does this compare to conventional surgery? We have a comparative conventional cohort. In the early phase of this, our clinical trials, we ran a bilateral study where we had a contralateral control arm. What I mean by that is that patients would come in, if they met all of the entry criteria to be enrolled in the study, they were randomly selected, so that one eye received conventional treatment with our system and the other eye received customized treatment. Again, the eyes were randomized.

Of that comparative arm, 50 eyes actually meet the criteria of being myopic with less than half a diopter of cylinder. So we went back and looked at all of the conventional patients that we treated in the early phases of the study and found out that 50 eyes met the criteria for our current conditions of approval, and you can see that the refractive parameters for that conventional comparative group match up very, very well with the primary

Custom cohort. Those patients also had a treatment optical zone of 6.5mm in diameter and we have wavefront data measured in the same way available preoperatively as well as the one- and three- and six-month postop intervals.

If we look at the aberrations in these two groups, the Custom shown by the blue bars and the 50-eye conventional comparative cohort shown by the red bars, preoperatively, the aberration content's relatively similar between these two groups. There was a small but statistically significant difference in the spherical aberration term but all other parameters were well matched. That's not the case when we look six months after surgery. Again, these asterisks indicate anything that exceeded the P value for statistical significance of being less than .05 and you can see that the total higher order, coma, trifoil, spherical aberration, and tetrafoil, are all significantly lower six months after wavefront-guided treatment than six months after conventional surgery. Secondary astigmatism term was also lower in the Custom eyes but that wasn't a statistically significant difference.

Now, we've tried to and we've worked with the agency and tried to come up with a way of describing what's the optical impact of the magnitude of these differences in the higher-order aberrations, and this again is an optical simulation of how a patient might see the eye chart under

best-corrected vision where the lower-order aberrations are removed. On the left, they're left with the postop aberration mean for wavefront-guided treatment, and on the right, they're left with the mean values for conventional surgery, and you can see there's a modest but definite difference with the optical quality being better in the wavefront-guided approach.

Now, that's all based on mean values. We also looked at on an individual patient basis what percentage of patients exhibited an actual decrease in the higher-order aberration parameter after surgery as compared to before, and so the different lines in this table indicate the various ways of looking at the higher-order aberrations for third and fourth order, and this middle column indicates the percentage of wavefront-guided eyes that showed a reduction in that particular parameter, and on the right-most column, we're looking at the conventional eyes, and you can see that for most of these parameters, much higher percentage of wavefront-guided patients actually showed a decrease six months after treatment as before surgery and that's not true in the conventional eye. The percentages are much lower.

I'd like to now invite Dr. Steve Brint to come up and talk about the clinical implications of the wavefront correction.

DR. BRINT: Thank you, Dr. Pettit.

I'm Steve Brint from New Orleans, Louisiana. I'm in private practice and on the faculty of Tulane University. I likewise am a member of the Alcon Medical Advisory Board. I've been performing LASIK since 1991 and am a LASIK patient myself, and I'm also the Medical Monitor of a competing laser technology and my expenses for this trip were also compensated by the sponsor.

As clinicians, we know that prior studies of conventional LASIK in general have shown that higher-order aberrations, particularly spherical aberration which is frequently linked to poor night vision, occasionally may be increased after conventional LASIK. These increased higher-order aberrations after conventional LASIK are pupil-size dependent with larger pupils showing decreased retinal image quality as measured by point spread function and modulation transfer function and visual performance as measured by the clinically useful contrast sensitivity testing and low-contrast visual acuity testing.

David Williams' group at the University of Rochester has done work in this area and has shown that correction of these higher-order aberrations using an adaptive optics system is able to improve the visual acuity and especially the contrast sensitivity.

As Dr. Pettit just mentioned, we do have this

comparative conventional cohort of 50 spherical myopic eyes that was derived as he mentioned which has comparable demographics and virtually identical preoperative refractive error. Quality of vision in this group was used just as we did in the wavefront-guided eyes using tests to determine the visual performance under these low-contrast and mesopic situations. I think we all realize as clinicians that we've done a very good job of getting good quantity at vision and now, as has been mentioned throughout the morning, the goal is not only to improve the quantity but improve the quality of vision for our patients.

So the contrast sensitivity testing was done using the VectorVision Chart, the CSV1000, measured at 3, 12 and 18 cycles per degree. This was done in both every-day full illumination to simulate a photopic situation as well as in a room with total darkness, other than the light coming from the eye chart, to simulate a mesopic light situation, and a neutral density filter was placed in front of the eye which only transmitted 3.16 percent of the light. We know that greater higher-order aberrations are seen in these larger dark-adapted pupils as opposed to the smaller light pupils.

Previous FDA studies have used a contrast sensitivity definition as a clinically significant change

of greater than 0.3 log units at two levels from preoperative at two or more spatial frequencies, and this is used to distinguish measurement noise from actual true sensitivity change. What we saw in our spherical cohort as regards to percentage of eyes with this clinically significant change of photopic contrast sensitivity, here in the Custom group of spherical eyes, we see two to three times gain as opposed to loss of contrast sensitivity and clinically significant contrast sensitivity, and in the conventionally treated eyes, we see actually at both the three- and six-month interval no gain and some loss of this clinically significant photopic contrast sensitivity.

The full eye larger cohort is nice in that it confirms what we saw before with a tendency towards gain as opposed to loss in the wavefront-treated eyes and loss as opposed to gain as treated in the conventionally treated eyes.

Looking at photopic contrast sensitivity another way, at individual spatial frequencies, we see conventionally treated eyes, no mean log change in the lower spatial frequencies and significant loss in the higher spatial frequencies. In the Custom group, however, we see gain across the board at all log changes at all spatial frequencies and this is statistically significant at the higher spatial frequencies of 12 cycles per degree

and 18 cycles per degree, and this is confirmed looking at the larger full eye group. In the conventional group, we see across the board at all spatial frequencies a trend towards loss of photopic contrast sensitivity as measured in log units and somewhat modest gain in the Custom-treated eyes.

As regards the clinically important mesopic contrast sensitivity, the large pupil at night time contrast sensitivity, important to our patients in tasks such as driving at night, we see, also, two to three times the number of eyes gaining clinically significant contrast sensitivity in the Custom group, both early and at the late testing intervals, while in the conventionally treated eyes, initially there's more loss. However, there is recovery in the later interval which simulates what we see in the six-month conventional group, what we see in the Custom group at three months, suggesting that these customized enjoy this improved mesopic contrast sensitivity throughout their recovery period without going through the decreased period that our conventional eyes have. This is confirmed once again in the all-eye group with improved mesopic contrast sensitivity and decreased at three months, recovers at six months, but once again is maintained throughout the entire postoperative period in our Custom wavefront-treated eyes.

Looking at mesopic contrast sensitivity in our conventional eyes, we see a modest gain at all spatial frequencies at six months. However, in the Custom-treated eyes, we see a much larger gain in the Custom-treated eyes as measured in log units over this period of time at six months at all spatial frequencies, and this once again is confirmed when we look at the larger cohort of all eyes wit these more difficult toric prescriptions.

Low contrast visual acuity was measured using the ETDRS eye chart. We're all familiar with the standard high contrast eye chart. You can all see how extremely difficult it is to see this 10-percent low contrast eye chart that was actually viewed in a room with ambient very dim light, and it should be noted that even in our preoperative best spectacle-corrected vision patients, only 8.6 percent of patients were able to read the 20/20 line preoperatively.

Looking at the change in the low contrast best-corrected vision in our spherical group, we see that there is more gain than loss at both the early as well as the later time interval, more so than we see in the conventional eye group, but more importantly, statistically significant, we see that there is significantly less loss in the Custom eye group at three months as compared to the conventional eye group, less loss of one or more lines from

preoperative value at 22 percent as opposed to 36 percent, and this approaches statistical significance. If we look at all the eye group, we see that this is even more statistically significant at both the early as well as later intervals, less loss of one or more lines of low contrast vision as compared to what we're used to seeing in our conventional eyes.

So in summary, of the Custom spherical eyes evaluated at the six-month time gate, as looking at photopic contrast sensitivity, we had 2.2 percent gain as opposed to 0.7 percent loss with a mean gain at all spatial frequencies. Looking at clinically important mesopic contrast sensitivity, we had 15.3 percent gain as opposed to 5 percent loss, and once again mean gain at all spatial frequencies, and with this extremely difficult low contrast best-corrected vision, we had one or more lines gained in 38.8 percent of the patients as compared to 20.9 percent loss.

So in conclusion, the Alcon CustomCornea System is unique in that it's capable of measuring each of these aberrations measured by the aberrometer and taking them and registering them to each other so that we have a very accurate composite aberrometry reading of both the low- and high-order aberrations of the entire optical system which we're then able to match and link and transfer to the

excimer laser, register it perfectly to the treatment of the excimer laser, which then calculates and delivers a specific ablation pattern unique for each individual eye. The ablation pattern is uniquely determined from these preoperative aberrations present in each individual eye.

Dr. Durrie has shown that wavefront-guided CustomCornea treatment easily meets all the FDA guidance criteria for safety with exceptional improvement of best spectacle-corrected vision, especially at the extremely high levels of acuity, 20/12, 20/16. Dr. Hakim has shown that the CustomCornea treatment exceeds all the effectiveness criteria as established by the FDA with a very, very precise type standard deviation around the mean. The Custom eyes have shown a consistent trend for more eyes to have a clinically significant gain as opposed to loss of both mesopic and especially photopic contrast sensitivity and more eyes have shown a gain of one line or more of low contrast best-corrected vision as opposed to loss.

Compared to these conventional eyes, the Custom eyes have a statistically significantly better mean photopic contrast sensitivity and as has been shown, we're able to preserve in the Custom eyes this mesopic contrast sensitivity at three months which is lost in the conventional eyes, although it does recover, but it allows the Custom eyes to enjoy excellent mesopic contrast

sensitivity throughout their recovery period and there is a statistically significant lower loss of low contrast best-corrected vision of one line or more.

We believe that wavefront-guided LASIK produces an eye that's optically superior to conventional LASIK, and for our patients, this means significantly less postoperative aberrations, as has just been shown in Dr. Pettit's presentation, and in these Custom eyes, we've seen a significantly greater reduction in the higher-order aberrations of virtually all of the specific types from preop as compared to what was seen in the conventionally treated eyes.

So I think from a clinical point of view, this is something that, as has been discussed this morning, is extremely important for improving the visual quality of our patients and in the future for perhaps going back and taking care of some of the problems as Mr. Link has previously discussed.

I think we have a little bit of time left to answer some of the questions that were specifically addressed by the panel. I'll turn the podium back over to Dr. Pettit.

DR. PETTIT: Thank you, Dr. Brint.

By my watch, I have eight minutes, and I'd like to just touch on some of the questions that the FDA and you

panel members have raised in reviewing some of this material.

I'd like to just start with Dr. Huang's review, and he noted that at three and six months, after a CustomCornea, only 78 and 82 percent of patients had a low contrast UCVA of 20/40 or better and only 5.8 percent achieved a low contrast UCVA of 20/20 or better and expressed some concern about that. We went back and looked at that data and found that that's actually a fairly unremarkable -- this is a relatively difficult test, and what I mean by that is if we look at the eyes preoperatively, best-corrected visual acuity of 20/20 or better, only 8.6 percent of the spherical eyes were able to see the 20/20 line on the eye chart. Three months after surgery, 5.8 percent of our patients were able to see that line, and at six months, it's 7.9 percent low contrast UCVA approaching their preop BCVA. Low contrast UCVA of 20/40 or better is actually slightly higher in the wavefront-guided-treated eyes at both three and six months than it is in our comparative conventional group.

In Dr. Bradley's review, he raised a very interesting question, and I'm paraphrasing it slightly here. He's basically asking are we correcting the aberrations that were in the eye before surgery? Are we compensating for the treatment-induced aberrations or are

we doing both? Well, in all honesty, we are attempting to do both, so that the postop aberrations are as small as possible.

When we began the wavefront development effort, our initial aim was simply to treat the preop aberrations. However, in our early trials, looking at the pre- and postop wavefront data, it became very clear that the aberrations induced by the surgery were also very important and some, not all, but some of these surgical effects were predictable, and therefore our Custom ablation algorithm evolved from one that simply calculated the profile directly from the wavefront data into one that took the wavefront data but then made some adjustments to the wavefront-based profile to compensate for predictable surgical effects. I just want to stress that all 139 eyes in this cohort were treated at the end of this process with a consistent algorithm.

Dr. Bradley went on to offer one analysis possibility that we could perform. How do we know if we're treating the preop aberrations? He suggested we look at the correlation between the aberrations before and after surgery, and if successful, the wavefront-guided postop aberrations should be uncorrelated with the preop eye-only aberrations. We did that analysis, and the correlation coefficients are shown here. This is looking at the

individual higher-order third- and fourth-order aberrations between preop and three months after surgery, preop and six months after surgery, and you can see down here for two of these fourth-order aberrations, there is a modest positive correlation coefficient, somewhere in the .4 to .45 range, but in general, these numbers are pretty small. Postop aberrations are not well correlated to the preop aberrations. That's not ironclad proof that we're treating the preop aberrations. I'm going to come back to that in just a second and say a little bit more.

How do we know that we're treating the surgically-induced aberrations? Well, we looked to see if there were any significant correlations between the lower-order aberration changes, the changes in the myopia, and changes in the higher-order aberrations, and we found there were no significant correlations between the lower- and the higher-order aberration changes. We also looked to see if there's any correlation between the clinical refraction changes and changes in the higher-order aberrations, and again we found no correlation between the higher-order aberrations and the refractive treatment effect. Neither of these findings is true for conventional surgery, and we've submitted a large body of data to the FDA over time showing the trends we see for conventional treatment. We don't see such coupling, so-called, effects here.

What I'm really trying to say is best summarized by this slide which I showed earlier. This is looking at the higher-order aberrations six months after surgery. The blue bars are the Custom outcomes, the red bars are the conventional 50-eye outcome. The surgical predictable effects that we include in the ablation algorithm involve only the rotationally symmetric terms. So on this chart, that only involved the spherical aberration term here. So the fact that we're having significant success in limiting the spherical aberration, I believe, is due to the fact that we're compensating for the surgical induction that would otherwise occur, but these other higher-order aberrations are not rotationally symmetric and there's no compensation mechanism folded into the treatment profile to deliberately counter these. So the fact that we see lower levels of these non-rotationally symmetric terms to me, I think, is the best evidence that by including them in the preop profile, we are effectively treating them, although not eliminating them.

One of the questions that the FDA is posing to the panel is are any of the differences between Custom and conventional outcomes clinically and/or functionally significant? I think Dr. Brint very nicely summarized what we think are the significant differences. Compared to conventional surgery, wavefront-guided-treated eyes have

significantly lower postop higher-order aberrations, significantly higher percentage of eyes with an actual reduction in various higher-order aberration parameters relative to preop. They have a statistically significantly better mean photopic contrast sensitivity and preservation of mesopic contrast sensitivity at three months where we see a consistent dip in the conventional treatments, and they have a statistically significant lower loss of low contrast BCVA defined as one or more lines.

Part of Question Number 3 for the panel asked what information about the measurement, analysis and correction of higher-order aberration is needed to accurately inform physicians and prospective patients about the safety and effectiveness? We've worked with the agency to try to come up with a simple means of describing the potential optical benefit of doing this type of surgery. We're going back to that optical simulation of what a high contrast chart would look like, and we come up with a difference between wavefront-guided and conventional treatment that corresponds approximately to about 2 diopters effective defocus blur. Under low contrast conditions, this would be a different outcome certainly.

DR. GRIMMETT: That would be .2.

DR. WEISS: Yes, I think you misspoke. I think you meant .2 rather than 2 diopters.

DR. PETTIT: I'm sorry. Point 2 diopters. Absolutely. That would be very nice.

(Laughter.)

DR. PETTIT: We're not there yet.

Question Number 4 for the panel talks about the refractive effects of correcting the higher-order aberrations and states that these are smaller than the effects of correcting the lower-order aberrations, suggesting that relatively modest instabilities of sphere and cylinder correction could disrupt the higher-order corrections.

There's two points I just want to touch on briefly here. Number 1. The wavefront-treated outcomes have the same refractive stability as conventional surgery. The higher-order aberrations in our wavefront population are at least as stable as the aberrations in conventionally treated eyes, and therefore we believe that modest versus large amounts of these higher-order aberrations should be beneficial to patients in the presence of refractive instability in the postoperative course.

Another final point is we looked at are the refractive instabilities somehow linked to higher-order instabilities? In other words, if the patient's myopia is changing in the postoperative interval, are the higher-order aberrations changing in any corresponding fashion?

No. That should be defined as a correlation analysis looking at the higher-order aberrations between three and six months, and we saw no significant correlation, no correlation larger than .18, between the refractive changes and the higher-order changes. We also looked at changes in the lower-order aberrations as measured by wavefront device, compared those to the higher-order aberration changes, and again saw no significant correlations.

That actually concludes our presentation. Thank you very much for your attention.

DR. WEISS: I'd like to thank the sponsor for their presentation.

We will take a 10-minute break. I'd ask everyone to be back here promptly so we can start exactly in 10 minutes, and we'll proceed with the meeting then.

Thank you.

(Recess.)

DR. WEISS: We will be starting now, if everyone is now seated. We're going to proceed with, for the next half hour, with the panel questions for the sponsor, and then we'll have the FDA presentation.

I would first like to ask the sponsor two questions. One. There was a cohort in which one eye had conventional treatment and one eye had customized treatment. Since a question the patients will ask is can I

notice any difference, aside from the numbers that we see, can the patients notice any difference, were those patients asked which eye they preferred, the customized corneal treatment eye or the conventional eye?

DR. PETTIT: We'll see if we can -- I'm not sure. Right. That's right. There are 50 eyes in the conventional arm of the study that meet the spherical definition. There are actually only 19 eyes that were treated conventionally in the spherical group. There were 19 patients that were treated one eye conventional and one eye with the Custom algorithm. So it's not 50 eyes. It's not 50 patients. It's only 19 where they actually were treated one eye one way and one eye the other, and we'll see if we can find information on those particular 19 eyes for you.

DR. WEISS: Okay. While we're waiting for that, I had a second question on one of the higher-order aberrations, the tetrafoil. Does this behave different than the other aberrations? For example, the conventional group actually had a higher percentage of eyes, 28 percent of eyes in the conventional group had a reduction in this particular higher-order aberration as opposed to 22 percent in the Custom group. So the conventional group had a greater percentage of people with reduction in this particular type of aberration, and in addition, on Table 4,

there is a continued reduction in this aberration which is statistically significant between three and six months. So it still is changing after the "eye" has stabilized refractively.

So I was wondering why. Is this different than the others, and does this treatment not treat this particular aberration, and if so, why not?

DR. PETTIT: Well, right. It's important to note that the average value, looking across the groups, the average values for the tetrafoil aberration were smaller in the wavefront-guided populations than they were in the conventional, but there was a slightly higher percentage of actually conventionally treated eyes that showed a reduction. So the mean value was less looking across the entire group. Slightly higher percentage of eyes, though, you're right, had a reduction in aberration.

The simple answer is the higher-order aberrations, they all have slightly different optical effects on image quality, and I think Dr. Burns or Dr. Bradley can very objectively speak to which aberrations potentially are the most detrimental. If I had to pick one that I wouldn't worry as much about, it actually would be the tetrafoil as opposed to some of the others. But certainly the panel members can speak to that very eloquently.

DR. WEISS: Thank you.

Dr. Huang?

DR. HUANG: I have a follow-up question on the first question Dr. Weiss raised.

There were only 50 patients had a treatment in one conventional and one eye with the Custom treatment, but on the table presented by Dr. Brint earlier this morning, there were several tables indicating that in all eyes group, there were N equal to about 420 some odd eyes in the Custom group and then in the conventional treatment, there were N equal to about 130 some odd eyes.

Was there a mistake in terms of the tabulation or was that --

DR. PETTIT: No, there was no mistake.

Again, we're seeking approval just for the spherical cohort. So those are eyes with less than half a diopter refractive cylinder. We've treated a much larger population of patients and contrast sensitivity. We have data on the entire eye cohort which includes myopes and astigmats. So if we include astigmatism, we have data on something like 426 wavefront eyes and 139 or something like conventional eyes.

For contrast sensitivity, which has historically been a safety parameter and is done under best-corrected conditions, we presented that information as

supportive of the trends that we saw in the primary cohort. So we have the primary cohort which is 139 Custom spherical eyes as compared to 50 conventional spherical eyes, but then supportive data on the larger body which includes astigmats and the Ns are larger for that reason.

DR. HUANG: Thank you.

DR. WEISS: Dr. Matoba?

DR. MATOBA: In looking at your protocol, I didn't see any reference to pupil sizes as either exclusion criteria or inclusion criteria. Is that taken into account when you were entering these patients?

DR. PETTIT: I have to defer.

DR. MATOBA: And the reason I ask is because the 50 patients who had the conventional ablation were done earlier in the study than the Custom ablation patients in general, correct? And I wondered if there might be a difference in the average pupil size between the two groups and that may affect patient satisfaction or other visual tests.

DR. PETTIT: Okay. The entry criteria did not change over the course of the study.

DR. MATOBA: If you didn't take pupil size into account, then how would you know what they may have been in those patients that were entered?

DR. PETTIT: We can look at pupil size. Do you

want to speak? Okay. Let me make sure I have the question down exactly right. For this conventional comparative group, did we control for pupil size or did we have an analysis baseline?

DR. MATOBA: I'm sorry. Go ahead.

DR. PETTIT: Well, I want to make sure I get it right. Did we analyze the data based on pupil size to see if there was any statistically significant difference in pupil size between those eyes and the wavefront group?

DR. MATOBA: Well, my main question is could there have been a significant difference in the average pupil size between the patients who had Custom ablation versus people who had conventional ablation?

DR. PETTIT: Okay. So you're concerned that there might be a significant difference in pupil size between the two groups?

DR. DURRIE: I can just comment from an investigator standpoint, is the inclusion criteria were the same throughout the study, and the conventional eyes were done fairly contemporary because initially we did a group with the same algorithm. We did a group that had one eye with conventional and the one eye with Custom. The reason that the number is small is when we drop it down just to spherical cohort, then it gets us down to only 50 eyes. So these were done at relatively the same time period. It's

not like one group was done three years ago and one group was done a year ago, and the inclusion criteria regarding pupil size was the same.

I think it is interesting, and I think it'd be a good thing to look at, is to actually analyze, since the aberrometer itself records pupil size, so that data is available, and it would be a good thing to continue to look at. I think with all these things, we're coming up with new things we can look at because now we have a digital instrument that can actually give us data that we haven't had before.

DR. WEISS: I'm going to ask members of the panel, for the purpose of the transcription, if they can identify themselves before they speak. The sponsor. Excuse me.

Dr. Bandeen-Roche?

DR. BANDEEN-ROCHE: Dr. Bandeen-Roche.

My question follows up on Dr. Weiss's first question and Dr. Huang's question. I think it's coming up repeatedly. If you could just clarify very explicitly this conventional cohort, you know, so they were selected early on in the study. To what extent was randomization involved in their selection versus the Custom eyes? Were they treated by all of the same physicians who treated the Custom eyes? Were there any differences with respect to

this cohort that could be expected to influence results, including practice effects, as the study went on? I know there were some differences in temperature and humidity. Pupil size has been raised, et cetera.

DR. PETTIT: Okay. I'm going to ask Dr. Christy Stevens, our Clinical Affairs Director, to come forward to talk about the inclusion criteria.

MS. THORNTON: Excuse me. I'd like to emphasize to the sponsor, the transcriber and summary writer have indicated that they would like very much to have help from the sponsor group and give your identification before you speak.

DR. STEVENS: Christy Stevens, Alcon.

The study started with a contralateral design with one eye Custom, one eye conventional, and it was randomized as to which eye would be the Custom treatment.

DR. WEISS: I wonder. Would you be able to get a little closer to the microphone and speak a little slower? Thank you very much.

DR. STEVENS: Do you need me to repeat what I just said?

DR. WEISS: I think it would be best. Yes, please.

DR. STEVENS: Okay. It was a contralateral study design when it began. One eye received Custom, one

eye received conventional, and it was randomized as to which eye received the Custom treatment.

When we started the study, we modified the Custom algorithm over the course of the early part of the study. So in our Custom cohort that you've seen presented, it contains the final algorithm, only contains the last algorithm, but we included all conventional eyes that were in the beginning of the study because they were all treated the same way.

DR. BANDEEN-ROCHE: And I thought I heard a comment that only 19 of the eyes were treated one eye one way and one eye the other. So who were the others?

DR. STEVENS: There were 50 spherical conventional eyes total, of which 19 had an algorithm or current algorithm, the last algorithm in Custom, that were also a spherical eye, and so yes, they were treated by the same centers with the same study protocol.

DR. BANDEEN-ROCHE: Thank you.

DR. WEISS: Thank you.

Mr. McCarley?

MR. McCARLEY: I had just a question about what effects have you considered or do you expect for a patient following cataract surgery? In other words, the mean on these patients was 36 years, I think, and assuming they're all phakic eyes, what happens when they're 70 or 75 and

have cataract surgery? Would they be expected to go back and have a reablation to address what had been corrected in their system, now that one of the components is missing?

DR. PETTIT: Yes, that's a good question, and the honest answer is we don't have any clinical data on patients that meet that criteria.

There is evidence in a young patient that the corneal aberrations are somewhat balancing compared to the internal aberrations and that, you know, obviously the situation's going to change very significantly when you go in and do cataract surgery. I think it's important to mention, though, that with our treatment, we are keeping the aberration magnitude comparable to what it was before surgery. We're not grossly changing the magnitude of the aberrations that were present in the eye beforehand. We're keeping them more like they were before treatment. So we don't anticipate that we're suddenly going to have all these new problems when the patients come back for cataract surgery.

Now, to get the best possible optical quality after cataract surgery, potentially sure, they might benefit by some kind of customized correction on top of that, but we don't have any clinical data that that's actually true.

DR. WEISS: Dr. Owsley and then Dr. Huang.

DR. OWSLEY: Thank you.

I just wanted to make sure I'm understanding your low contrast acuity data properly. It appears that whether we look at the sphere analysis or the all eyes analysis, 20 percent or one in five patients experienced a loss in low contrast acuity. I know that's different, lower than the rate in the conventional surgery, but I just want to make sure I understand. Twenty percent of the patients, one in five, experienced at least a one line or greater loss?

DR. PETTIT: That is correct.

DR. OWSLEY: Thank you.

DR. WEISS: Dr. Huang, please.

DR. HUANG: I just want to ask. Since we set out to try to correct the higher-order aberrations by this application, but the end result shows that there were general increase of the higher-order aberrations, and I don't know if the clinicians or the sponsor have any kind of comment regarding the outcome.

DR. PETTIT: It is true that even after our wavefront-guided surgery, that the higher-order aberrations are generally higher. They're higher by an amount that's significantly much less than what we get with our conventional surgery. We believe that's beneficial to the patient.

Our theoretical endpoint is to make them zero, and we clearly are not achieving that yet, but by shooting for that as the theoretical target, we are limiting what happens to them and that's where we are with the current state of the technology.

DR. HUANG: But my point is, instead of reducing, now we are actually increasing. So what's the future direction in that regard?

DR. DURRIE: Dan Durrie.

From a clinical standpoint, this is a step along the way because before we weren't even measuring the patient's preoperative aberrations, other than sphere and cylinder. Now we're finding other things that we find clinically significant in the population now that the aberrometer can measure.

As George said in his presentation about the progress, we found out then that there was some surgically-induced aberrations and some of them were predictable. I think as time goes on, we will learn more about the surgically-induced aberrations and then may have to make compensations. I think it's going to be important for all of us to start thinking about how are we going to accomplish that from a regulatory standpoint when you come up with the next new iteration, so it isn't so onerous that the companies cannot pursue that, and it isn't too onerous

from a regulatory standpoint, and I think it's something that I know that you're having a meeting tomorrow to talk about phakic eye welds, but I'd certainly like to have us continue to have a discussion between the sponsors and the clinicians and the agency about once we get better, what do we do then? Because I think this is a step along the way, but we still would like to make that zero, and we're going to have to continue to evaluate data in order to make that happen.

DR. WEISS: Dr. Burns, and then Dr. Bandeen-Roche.

DR. BURNS: Yes. Your sample had a very low percentage of Asians in it, yet it's a high-refractive error group, and I just wondered if you had a comment.

DR. PETTIT: I think the race distribution in the study was comparable to that we've seen in prior studies. Do we have any further comment? I mean, there was no attempt to include or specifically recruit certain patient populations or not. This is just the patients that came in, were interested in being in the trial and met all of our inclusion criteria.

DR. WEISS: Dr. Roche?

DR. BANDEEN-ROCHE: Dr. Bandeen-Roche.

I have a question that goes to the fact that relatively few sites participated in the study. So you

provided the site distribution of all eyes and it ranged from 36 percent in the provider who did the most to about 10 percent in the provider who did the least.

Do you have the same distribution for the spherical eyes and also the distribution of the conventional, the 50 conventional eyes by site?

DR. PETTIT: We'll see what we can dig up in that regard.

DR. BANDEEN-ROCHE: And finally, can you describe how the sites were selected and what training, just very briefly, the extent of training that the physicians received?

DR. PETTIT: The site selection criteria, we obviously were interested in trying to get innovators in this field, high-volume/high-profile refractive surgeons that were knowledgeable about new advances in technology. I don't know that there was anything beyond that. It was as simple as these doctors seemed to be very well qualified and were interested in participating in the study, and we wanted to work with them.

The training that they received, they obviously received some training in how to use the wavefront device. The treatment aspects are very similar to what they were already using for their conventional LADARVision treatments. There was a slight difference in the fact that

they had to mark all patients before treatment as opposed to just spherical patients in their conventional surgery, those little eye marks they put on the eye, and then the reticle that came up during treatment, the software image projected into the LADARVision tracked image screen was slightly different, but the other aspects of the treatment were really identical to what they'd seen before.

We did spend some time going through them, the meaning of the wavefront measurements and, you know, when their clinician brought them data, what did that mean for that patient in terms of relative to the foropter, for example?

DR. WEISS: Dr. Grimmett, and then Dr. Matoba.

DR. GRIMMETT: Dr. Michael Grimmett.

I just had an observation and would like to hear if you have a comment. You may have none. There may be no answer.

I found it curious that despite a very comprehensive analysis and sophisticated technology, that the patients that were unsatisfied or extremely unsatisfied approximated 9 percent. It's notable that the PERK study by comparison, using bear skins and stone knives, had an 11-percent dissatisfaction rate, and I found it curious that one in 10 patients are unsatisfied, despite a phenomenal amount of technology and analysis, and I would

like to commend you on a superb analysis and presentation.

Do you have a comment why it's still one in 10 despite all the sophisticated technology or is there no answer to that, sir?

DR. PETTIT: No. Well, I don't know everything. I didn't personally speak to these patients. I think one factor was that they tended to be a little bit undercorrected. The patients that were undercorrected on average were less satisfied than the patients that were right on, and again there's no latitude for the surgeon trying to optimize the refractive outcome. We wanted everything done exactly the same way and that led to a slight undercorrection, and the patients where that undercorrection was more than the mean, they ended up more myopic than the mean, they tended to be less satisfied.

I think, you know, in all honesty, in addition, there's a lot of hype surrounding this procedure, and I think their expectation levels in some cases was pretty high, but, you know, that's not scientific. That's just an opinion.

DR. HAKIM: If I could just add to Dr. Pettit's comments, I mean, I agree that --

DR. WEISS: Could you introduce yourself, please?

DR. HAKIM: Omar Hakim. Sorry. Omar Hakim.

I just want to add and really reinforce George's comments, you know, about the undercorrection aspect of this. We weren't able to make any adjustments as we normally do when we do surgery, and clearly there was a difference in the patients who were satisfied versus dissatisfied with their surgery, based on their residual refractive error, and the expectation issue, I think, you know, is a very big issue. I literally had patients coming back who were now seeing 20/16 uncorrected acuity and wanted enhancements. So their expectations of the surgery clearly were raised as well as in the minds of their own physicians who had referred them. They were talking about supervision and the Popular Science article last March, you know, talking about the ability to give people, you know, better than 20/10 or 20/8 or 20/6 vision.

Clearly, what we really want to do is avoid problems, you know, like Ron Link talked about this morning, is try to create better quality of vision, and as Dan Durrie was saying, this is really a process in evolution, but if I could have my surgery done again today and avoid the induction of these higher-order aberrations that we create whenever we do conventional surgery, that's what I would choose for myself and all my patients.

DR. PETTIT: Just to follow up a little bit on an earlier question. This is George Pettit from Alcon.

I think Dr. Matoba asked the question about the pupil sizes and were the patients informed. Given this high-level expectation, it's important to note that the optical zone was 6.5mm and we informed all patients considering being in the trial that if their natural pupil was larger than 6.5mm, even with this new technology, there was a potential risk for them to have night vision symptoms. So we tried to bring their expectations more in line.

DR. WEISS: Dr. Grimmett has a follow-up question.

DR. GRIMMETT: I have just a simple operational question.

Is this software that's going to be retrofitted to existing product base, the LADARVision 4000s out there? Does this require a whole investment in brand-new technology?

DR. PETTIT: No, from the LADARVision side, it's a simple software upgrade.

DR. WEISS: Dr. Matoba?

DR. MATOBA: Alice Matoba.

I actually was going to refer to the same chart for the table on Patient Satisfaction and also the previous page on Patient Symptoms. Do you have these same data for the people who were treated with the conventional laser?

DR. PETTIT: So the question is do we have the patient satisfaction questionnaire-type data for the patients treated conventionally?

DR. MATOBA: And also symptoms at six months.

DR. PETTIT: And do we have data on the conventional patient symptoms at six months? We'll see what we have in that regard.

DR. WEISS: Dr. Bradley was next, then Mr. McCarley, Dr. Swanson, and Dr. Owsley.

DR. BRADLEY: Dr. Bradley.

I'm just curious about the apparent huge discrepancy between what Ron Link presented earlier today and the data on the symptoms presented by the sponsor. For example, Ron Link indicated that dryness and double vision are huge problems, and I think we have a couple of other people indicating that, and I look at the data you just presented on dryness where we have slightly more patients indicating worse dryness than those indicating better, and we have a very small number indicating increased double vision, about the same as those who are indicating decreased double vision.

So from the sponsor's dataset, it appears that we don't have this very large and disturbing incidence of dry eye and optical problems, such as double vision, whereas Ron Link and a couple of the other presenters

indicated that these are very serious problems, and I wondered therefore if we could clarify perhaps some inclusion criteria from the sponsor because one wonders if Mr. Link's dataset is rather biased to those who have the problems and somehow you have been able to effectively filter these people out of your datasets. Yours are biased the other way.

I think it's very important to get a sense of that, particularly for those people who are going to utilize this technology, and if you have effectively avoided these problems by your patient selection criteria, then this clearly should be included in the final labeling for this device.

DR. PETTIT: Dr. Durrie, would you like to comment?

DR. DURRIE: Yes. I'd really like to address that, and this is Dan Durrie.

Ron's website, which is where he gets his data, are for people who've had surgery and by its own definition and its goal, it's for people who have problems with refractive surgery, and I really appreciate the work that he's done on helping us define of those patients who have problems with refractive surgery, what are their problems, and obviously 25 percent of those problems are persistent dry eyes. But this is a very selected group not only

that's had refractive surgery but is self-defined that they have problems and they're logging into the website. So I think that's a defined group on that side.

On our side, I think that the only criteria that I think is significant from my clinical experience is the average age of this group was 38 years old, and we know that the patients, if I did LASIK on an average age of 55-year-olds, they'd have more problems with dry eyes. So I think that if there's a self-selection in this, there certainly wasn't anything in the screening from the standpoint of we had healthy eyes, there wasn't any tear film screening or any special testing, but I think that you do have a healthy eye group that's screened for a clinical trial that certainly is a healthy eye group and on the other side, in the surgical eyes group, you have the group that basically is having problems, and I think both those datasets are important.

I'd like to also, because I did look this up during the discussion, is if we take the 426 eyes that are available for analysis and run that same grid, that total grid of symptoms, the numbers are essentially identical. So here, you have -- which was requested really by the public presenters -- a very good dataset with a 100-percent follow-up on 426 eyes that gives you an array of symptoms on how many patients were the same, better or worse, and I

think that could be a dataset for labeling that could give you some good information with peer data because it does have 100-percent follow-up and it was done under a controlled fashion.

DR. WEISS: Dr. Bradley has a follow-up.

DR. BRADLEY: From your reply, you seem to be saying you've done nothing special to avoid these dry eye or night vision, double vision problems. Did I understand that correctly?

DR. DURRIE: In patient selection.

DR. BRADLEY: Second question, and this is really to --

DR. PETTIT: Dr. Bradley?

DR. BRADLEY: Yes?

DR. PETTIT: Could I just perhaps follow up? This is again fairly much just conjecture on my part, but the patients that participated in this study had to be willing to come back for many, many follow-up visits. So perhaps we, without attempting to, screened for a more educated or, you know, patients that really wanted this type of procedure and knew what the risks were ahead of time, I don't know, but they weren't just your standard patient coming in off the street that weren't going to have to go through all these tests for six months.

DR. BRINT: I think my comment is similar to